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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,700	09/24/1999	KARL-HERMANN SCHLINGENSIEPEN	P63763US0	5460

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	28

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding:

Office Action Summary	Application No. 09/341,700	Applicant(s) Schlingensiepen et al
	Examiner Jane Zara	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 3, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *59-78* is/are pending in the application.

4a) Of the above, claim(s) *59-69 and 78* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *70-77* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendments and response filed January 3, 2003 has been received and entered.

Claims 59-78 are pending in the instant application.

Election/Restriction

Newly submitted claim 78 (and previously submitted claims 59-69) are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The original election of SEQ ID NO: 1754 was made in the communication filed October 30, 2001, Paper No. 22.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 59-69 and 78 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of James and Stull et al, the combination in view of Probst et al, Crooke, Baracchini and de la Monte et al.

The claims are drawn to a method of selecting and preparing antisense oligonucleotides comprising at least 8 nucleobases whereby the oligonucleotides do not contain 4 or more consecutive elements capable of forming three hydrogen bonds each with 4 or more consecutive cytosines, and whereby the oligonucleotides do not contain two or more series of three consecutive elements capable of forming hydrogen bonds each with three consecutive cytosines, and whereby the ratio of C's or G's/(G's or C's) + (A's or T's) is greater than 0.29, more preferably between 0.33 and 0.86, which oligonucleotides further comprise modified bases, sugars or internucleotide linkages, and optionally comprise a covalently linked folic acid or hormone and a lipid.

James teach methods of selecting effective antisense reagents to target genes of known sequences, which oligonucleotides may further comprise nuclease stabilizing sugars such as 2'O-methyl substituted sugars, base or internucleoside modifications such as phorphorothioate internucleotide linkages, and which oligonucleotide compositions may further comprise covalently linked lipids (See entire text of James, especially pages 193, 197-198).

Stull et al teach methods of designing optimal antisense comprising providing indices for predicting antisense efficacy, which indices calculate contributions attributed to the strength of secondary structure at the target sites of RNA, a duplex score which estimates the ΔG formation for antisense target sequence duplexes, and a competition score which represents the difference between the duplex and secondary scores. Stull et al teach the use of such indices in predicting potential antisense efficacy within a target sequence for the preparation of antisense oligonucleotides comprising at least 8 residues, a maximum of twelve elements which are capable of forming 3 hydrogen bonds to cytosine bases, but does not contain 4 or more consecutive elements, does not contain 2 or more series of 3 consecutive elements, comprises a ratio of 3H bond forming elements to total nucleotides between 0.33 and 0.86 (see entire document, especially tables 1-5, and the oligonucleotide sequences therein, on pages 3504-3507).

The primary references do not teach preferred antisense subsequences which enhance antisense or nonantisense effects of oligonucleotides, nor do they teach the cellular cytotoxicity of antisense in relation to specific guanosine content or configurations, nor the incorporation of 2'-O-methoxyethoxy sugar substitutions into oligonucleotides.

Probst et al teach sequence the unpredictability of antisense oligonucleotides comprising self associating G-rich sequences and non-antisense effects of G-rich sequences and G-tetrads (see especially page 290).

Crooke (Ann. Rev. Pharmacol. Toxicol., Vol. 32, pages 329-377,1992) teaches methods for the preparation of antisense oligonucleotides comprising at least 8 residues, a maximum of twelve elements which are capable of forming 3 hydrogen bonds to cytosine bases, but does not contain 4 or more consecutive elements, does not contain 2 or more series of 3 consecutive elements, comprises a ratio of 3H bond forming elements to total nucleotides between 0.33 and 0.86, optionally comprises internucleotide, sugar and/or nucleobase modifications for enhancing stability against nucleases, and optionally comprises covalently linked hormones, peptides or phospholipids (See entire document, especially table 3 on page 335; last two paragraphs on page 335-first two paragraphs on page 337; compounds 1787, 1788, 1795 and 1796 in table 4 on page 345; first full paragraph on page 346; and first three full paragraphs on page 361).

Baracchini et al teach methods for the preparation of antisense oligonucleotides comprising at least 8 residues, a maximum of twelve elements which are capable of forming 3 hydrogen bonds to cytosine bases, but does not contain 4 or more consecutive elements, does not contain 2 or more series of 3 consecutive elements, comprises a ratio of 3H bond forming elements to total nucleotides between 0.33 and 0.86, optionally comprises internucleotide, sugar and/or nucleobase modifications for enhancing stability against nucleases, which sugar modifications include 2'-O-methoxyethoxy substituted sugars, and optionally comprises covalently

linked hormones, peptides or phospholipids (See entire document, especially col. 6-9; SEQ ID Nos: 16 and 20).

De la Monte et al teach the conjugation of hormones to antisense oligonucleotides for enhanced cellular uptake (See col. 29, lines 1-20).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to design and prepare optimal and effective antisense oligonucleotides for targeting and inhibiting the expression of genes of known sequence, with a reasonable expectation of success, because such techniques had been taught previously by James and Stull, and were routine methods in the art at the time the invention was made. One of ordinary skill in the art would have been motivated to exclude self associating G rich motifs within antisense because Probst et al teach the unpredictability of incorporating such motifs (including multiple G-tetramers) within antisense oligonucleotides. One of ordinary skill in the art would have expected that antisense oligonucletoides exert effects in both a non-specific and sequence specific way relative to the target gene sequence, as taught previously by Stull et al and Probst et al, which non-specific effects have been observed in vitro cellular toxicity studies, and which toxicity or alternative biological effects have been correlated with G-rich regions, One of ordinary skill in the art would have been motivated to design and utilize antisense oligonucleotides comprising less than 2 G triplets, and comprising one or no G tetramers, because the sequences of optimal antisense oligonucleotide sequences for a given target gene have routinely lacked such sequence configurations, as taught previously by Crooke (i.e. Table 4 on page 345), Baracchini (i.e. Seq ID

Nos: 16 and 20) and Stull et al (i.e. Tables 1-5 on pages 3504-3507). Furthermore, one of ordinary skill in the art would have been motivated to reduce toxicity effects of antisense by reducing the number of G-tetrads within an antisense construct because the correlation between G-rich content, cytotoxicity and other nonantisense biological effects have been taught by Stull et al and Probst et al, and antisense oligonucleotides avoiding such configurations have been routinely taught by many in the field, including Crooke and Baracchini. One of ordinary skill in the art would have been motivated to incorporate sugar, nucleobase and internucleotide modifications into antisense oligonucleotides, as well as conjugating biological effector molecules such as hormones onto antisense oligonucleotides, because such modifications have been shown to enhance oligonucleotide stability, enhance cellular uptake, target binding, and enhance the biological effectiveness of antisense, as taught previously by James, Baracchini, Crooke and de la Monte.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ram R Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER

JZ

March 10, 2003